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Supplementary appendix

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Supplementary Appendix

Supplement to: Methotrexate and Tumor Necrosis Factor Inhibitors affect Long-Term Immunogenicity to COVID-19 Vaccination in Patients with Immune-Mediated Inflammatory Disease

All data relevant to the study are included in the article or uploaded as supplementary information. Further de-identified data can be made available upon request via email to the corresponding author.

TABLE OF CONTENTS

Supplementary Methods

Participants
Established patients with IMID (n=245) receiving immunomodulatory treatment participating in the SAGA (Serologic Testing And Genomic Analysis of Autoimmune, Immune-Mediated, and Rheumatic Patients with COVID-19) study at New York University Langone Health in New York City,[5] who were scheduled for COVID-19 vaccination were assessed at 4-week, 3-month, and 6-month timepoints after the first vaccine dose from December 23, 2020 through December 1, 2021. Healthy subjects served as controls (n= 27). Seven patients with IMID received the NJN-78436735 viral vector vaccine. The remaining patients and all healthy controls received mRNA vaccines (BNT162b2 and mRNA-1273) and completed both doses of the series; none received additional doses (i.e., boosters). This study was approved by NYU IRB (20-01078).

Humoral immune response to COVID-19 Vaccine
Humoral immune response was assessed by testing IgG antibodies against the S1 domain of the spike protein of SARS-CoV-2 and percent of antibodies with neutralizing capacity.[6] IgG antibodies were measured using the QuantiVac ELISA test system (Euroimmun, Lübeck, Germany).[7] Adequate response was defined as greater than 5,000 RU/ml.[2] The percent of antibodies with neutralizing capacity was detected using the SARS-CoV-2 NeutraLISA (Euroimmun, Lübeck, Germany) with adequate response defined as greater than or equal to 35% as per manufacturer's instructions.

Statistical Analysis
Patient characteristics were summarized using means, standard deviations, and percentages as appropriate. Chi squared tests of independence and Fisher's exact tests were used for categorical variables between groups; Kruskal-Wallis tests for continuous variables. Associations of seropositivity rates with medication were assessed using separate logistic regression models among IMID patients, adjusting for age and sex; odds ratios and 95% confidence intervals were reported. A two-tailed p value of less than 0.05 was considered statistically significant. Correlation was determined using Pearson correlation coefficient. All analyses were performed using R v4.1.0 software (R Foundation for Statistical Computing) and GraphPad Prism v9.3 (GraphPad Software).

Supplementary Table 1. Baseline characteristics of entire cohort at 4-Week Timepoint.

Characteristic	Healthy (n = 27)	Patients (n= 245)
Age- mean (SD)	51.6 [13.2]	47.3 [15.6]
Female- n (%)	16 (59.3)	150 (61.2)
Male- n (%)	11 (40.7)	95 (38.8)
Race- n (%)		
White	17 (63.0)	191 (78.0)
Black	1 (3.7)	19 (7.8)
Asian	9 (33.3)	19 (7.8)
Other	0 (0.0)	16 (6.5)
Hispanic ethnicity- n (%)	1 (3.7)	36 (15.0)
Primary IMID - n (%)		
Psoriasis and/or Psoriatic Arthritis	--	64 (26.1)
Rheumatoid Arthritis	--	74 (30.2)
Crohn's Disease		45 (18.4)
Ulcerative Colitis		39 (15.9)
Other*	--	23 (9.4)
Long term medication- n (%)		
Methotrexate	--	84 (34.3)
Other oral DMARD#		39 (15.9)
Tumor necrosis factor inhibitor	--	100 (40.8)
Janus kinase inhibitors	--	15 (6.1)
Interleukin 17 blockers	--	13 (5.3)
Interleukin 23 blockers^	--	12 (4.9)
CD-20 depleting therapy	--	5 (2.0)
Glucocorticoids|	--	15 (6.1)
Previous COVID-19 - n(%)	5 (18.5)	48 (19.6)

[+]IMID denotes immune mediated inflammatory disease, DMARD disease modifying anti-rheumatic drug
*Vasculitis, dermatomyositis, adult onset stills disease, sarcoidosis, and polymyalgia rheumatica.
#Leflunomide, sulfasalazine azathioprine, hydroxychloroquine, mercaptopurine.
^Includes interleukin 12/23 blockers.
|Mean glucocorticoid was prednisone 13 +/- 10 mg (or equivalent).

Supplementary Table 2. Characteristics of cohort at 3-Month and 6-Month Timepoints

Characteristic	3 Months		6 Months	
	Healthy (n = 25)	IMID (n= 217)	Healthy (n= 26)	IMID (n=170)
Age- mean (SD)	52.5 [13.3]	48.2 [15.5]	52.1 (13.1)	48.1 (15.2)
Female- n (%)	15 (60.0)	139 (64.1)	15 (57.7)	114 (67.1)
Male- n (%)	10 (40.0)	78 (35.9)	11 (42.3)	56 (32.9)
Race- n (%)				
White	17 (68.0)	170 (78.4)	17 (65.4)	125 (73.5)
Black	0 (0.0)	17 (7.8)	0 (0.0)	17 (10.0)
Asian	8 (32.0)	15 (6.9)	9 (34.6)	17 (10.0)
Other	0 (0.0)	15 (6.9)	0 (0.0)	11 (6.5)
Hispanic ethnicity- n (%)	1 (4.0)	34 (16.0)	1 (3.8)	25 (14.9)
Primary IMID - n (%)				
Psoriasis and/or Psoriatic Arthritis	--	57 (26.2)	--	47 (27.6)
Rheumatoid Arthritis	--	66 (30.4)	--	53 (31.2)
Crohn's Disease		40 (18.4)	--	28 (16.5)
Ulcerative Colitis		35 (16.1)	--	22 (12.9)
Other*	--	19 (8.9)	--	20 (11.8)
Long term medication- n (%)				
Methotrexate	--	77 (35.5)	--	61 (35.9)
Other oral DMARD#		37 (17.1)		36 (21.2)
Tumor necrosis factor inhibitor	--	85 (39.2)	--	66 (38.8)
Janus kinase inhibitors	--	11 (5.1)	--	8 (4.7)
Interleukin 17 blockers	--	10 (4.6)	--	12 (7.1)
Interleukin 23 blockers^	--	10 (4.6)	--	4 (2.4)
CD-20 depleting therapy	--	4 (1.8)	--	5 (2.9)
Glucocorticoids	--	12 (5.5)	--	13 (7.6)
Previous COVID-19 - n(%)	4 (16.0)	40 (18.4)	5 (19.2)	27 (15.9)

[+]IMID denotes immune mediated inflammatory disease, DMARD disease modifying anti-rheumatic drug
*Vasculitis, dermatomyositis, adult onset stills disease, sarcoidosis, and polymyalgia rheumatica.
#Leflunomide, sulfasalazine azathioprine, hydroxychloroquine, mercaptopurine.
^Includes interleukin 12/23 blockers.

Supplementary Table 3. Adequate humoral response rate by disease state at all timepoints.

	4 Weeks			3 Months			6 Months		
	N	Adequate Humoral Response[#] (%)	P	N	Adequate Humoral Response (%)	P	N	Adequate Humoral Response (%)	P
Healthy	27	96.3	REF	25	100.0	REF	26	65.4	REF
All IMID*	245	88.2	0.331	217	88.9	0.147	170	56.5	0.523
UC	39	92.3	0.639	35	91.4	0.258	22	72.7	0.756
Crohn's	45	95.6	1.000	40	95.0	0.519	28	53.6	0.418
PsO/PsA	64	87.5	0.271	57	84.2	0.051	47	48.9	0.223
RA	74	82.4	0.105	66	89.4	0.183	53	54.7	0.468
Other[+]	23	87.0	0.322	16	84.2	0.073	20	65.0	1.000

* IMID denotes immune mediate inflammatory disease, UC ulcerative colitis, PsO/PsA psoriasis and/or psoriatic arthritis, RA rheumatoid arthritis.
[+] Vasculitis, dermatomyositis, adult onset stills disease, sarcoidosis, and polymyalgia rheumatica.
[#] Adequate humoral response defined as Spike IgG titer greater than or equal to 5000 RU/ml.

Supplementary Table 4. Humoral response by previous COVID-19.

	4 Weeks			3 Months			6 Months		
	No COVID (n=219)	Prior COVID (n=53)	P	No COVID (n=195)	Prior COVID (n=47)	P	No COVID (n=159)	Prior COVID (n=37)	P
Spike specific SARS-CoV-2 antibody titers—mean (SD)	19210.6 (7923.6)	23302.0 (7179.9)	<0.001	13114.9 (6033.9)	17991.3 (6032.7)	<0.001	6726.0 (5572.8)	13048.1 (6622.5)	<0.001
Adequate humoral response[X]—n(%)	192 (87.7)	50 (94.3)	0.223	173 (88.7)	45 (95.7)	0.182	81 (50.9)	32 (86.5)	<0.001
Neutralization antibodies (%)—mean (SD)	81.1 (31.4)	90.6 (21.8)	<0.001	78.4 (25.6)	898 (18.5)	<0.001	50.3 (34.5)	81.9 (25.6)	<0.001
Adequate neutralizing response—n(%)	187 (85.4)	49 (92.5)	0.257	173 (88.7)	45 (95.7)	0.182	95 (59.7)	33 (89.2)	<0.001

[X]Adequate humoral response defined as antibody titers greater than 5000 RU/ml. Adequate neutralizing response defined as greater than or equal to 35%.

Supplementary Table 5. Humoral response rates in patients with IMID on methotrexate compared to healthy controls and IMIDs not taking methotrexate.

	4 Weeks				3 Months				6 Months			
	Healthy (n=27)	No MTX (n=161)	Yes MTX (n=84)	p	Healthy (n=25)	No MTX (n=140)	Yes MTX (n= 77)	P	Healthy (n=26)	No MTX (n=109)	Yes MTX (n=61)	P
Age—mean (SD)	51.6 (13.2)	43.3 (14.6)	54.9 (14.5)	<0.001	52.5 (13.2)	44.2 (15.2)	55.4 (13.4)	<0.001	52.1 (13.2)	44.8 (15.1)	54.1 (14.1)	0.001
Female—n(%)	16 (59.3)	86 (53.4)	64 (76.2)	0.002	15 (60.0)	79 (56.4)	60 (77.9)	0.006	15 (57.7)	66 (60.6)	48 (78.7)	0.037
Race—n(%)				0.002				0.001				0.014
White	17 (63.0)	128 (79.5)	63 (75.0)		17 (68.0)	113 (80.7)	57 (74.0)		17 (65.4)	83 (76.1)	42 (68.9)	
Black	1 (3.7)	10 (6.2)	9 (10.7)		0 (0.0)	7 (5.0)	10 (13.0)		0 (0.0)	10 (9.2)	7 (11.5)	
Asian	9 (33.3)	10 (6.2)	9 (10.7)		8 (32.0)	8 (5.7)	7 (9.1)		9 (34.6)	8 (7.3)	9 (14.8)	
Other	0 (0.0)	13 (8.1)	2 (2.4)		0 (0.0)	12 (8.6)	2 (2.6)		0 (0.0)	8 (7.3)	3 (4.9)	
Hispanic—n(%)	1 (3.7)	19 (12.2)	17 (20.2)	0.079	1 (4.0)	19 (14.0)	15 (19.5)	0.164	1 (3.8)	15 (14.0)	10 (16.4)	0.580
Primary IMID*—n(%)				<0.001				<0.001				<0.001
UC/Crohn's	—	81 (50.3)	3 (3.6)		—	73 (52.1)	2 (2.6)		—	49 (45.0)	1 (1.6)	
PsO/PsA	—	39 (24.2)	25 (29.8)		—	34 (24.3)	23 (29.9)		—	28 (25.7)	19 (31.1)	
RA	—	25 (15.5)	49 (58.3)		—	22 (15.7)	44 (57.1)		—	20 (18.3)	33 (54.1)	
Other[+]	—	16 (10.0)	7 (8.3)		—	11 (7.9)	8 (10.4)		—	12 (11.0)	8 (13.1)	
Other Medication—n(%)												
TNFi	—	63 (39.1)	37 (44.0)	0.495	—	55 (39.3)	30 (39.0)	1.000	—	40 (36.7)	26 (42.6)	0.512
IL-17	—	12 (7.5)	1 (1.2)	0.039	—	8 (5.7)	2 (2.6)	0.500	—	9 (8.3)	3 (4.9)	0.541
IL-23[^]	—	12 (7.5)	0 (0.0)	0.010	—	10 (7.1)	0 (0.0)	0.016	—	4 (3.7)	0 (0.0)	0.298
JAKi	—	11 (6.8)	4 (4.8)	0.589	—	10 (1.7)	1 (1.3)	0.102	—	6 (5.5)	2 (3.3)	0.713
Glucocortcoids	—	12 (7.5)	3 (3.6)	0.275	—	9 (6.4)	3 (3.9)	0.551	—	10 (9.2)	3 (4.9)	0.382
Other DMARD	—	25 (15.5)	14 (16.7)	0.855	—	27 (19.3)	10 (13.0)	0.263	—	23 (21.1)	13 (21.3)	1.000
Held at least one dose of MTX	—	—	37 (44.0)		—	—	31 (40.3)		—	—	19 (31.1)	
Prior COVID-19—n(%)	5 (18.5)	34 (21.1)	14 (16.7)	0.740	4 (16.0)	28 (20.0)	12 (15.6)	0.731	5 (19.2)	21 (19.3)	6 (9.8)	0.236
Spike specific SARS-CoV-2 antibody titers—mean (SD)	20636.6 (5499.3)	21428.88 (7189.7)	17082.1 (9163.9)	0.001	16006.2 (5445.6)	14005.1 (6148.4)	13534.1 (6839.5)	0.326	7583.1 (5033.2)	8713.1 (6451.7)	6644.7 (6306.0)	0.084
Adequate humoral response[x]—n(%)	26 (96.3)	150 (93.2)	66 (78.6)	0.002	25 (100.0)	127 (90.7)	66 (85.7)	0.100	17 (65.4)	68 (62.4)	28 (45.9)	0.079
Neutralization antibodies (%)—mean (SD)	90.9 (19.3)	87.2 (25.9)	72.2 (36.8)	<0.001	87.4 (16.1)	81.9 (24.7)	76.0 (26.9)	0.228	58.5 (29.4)	61.0 (35.0)	47.0 (36.6)	0.074
Adequate neutralization response[x]—n(%)	26 (96.3)	145 (90.1)	65 (77.4)	0.009	25 (100.0)	128 (91.4)	65 (84.4)	0.052	18 (69.2)	77 (70.6)	33 (54.1)	0.09

* IMID denotes immune mediate inflammatory disease, UC ulcerative colitis, PsO/PsA psoriasis and/or psoriatic arthritis, RA rheumatoid arthritis, TNFi tumor necrosis factor inhibitor, IL-17 interleukin 17 inhibitor, IL-23 interleukin 23 inhibitor, JAKi janus kinase inhibitor, MTX methotrexate, DMARD disease modifying anti-rheumatic drug.
[+] Vasculitis, dermatomyositis, adult onset stills disease, sarcoidosis, and polymyalgia rheumatica.
[x] Adequate humoral response defines as antibody titers greater than 5000 RU/ml. Adequate neutralization response defined as greater than 35%.
[^] Includes Interleukin12/23 blocking agents.

Supplemental Table 6. Adequate humoral response rates by medication use at all timepoints.

	4 Weeks			3 Months			6 Months		
	N	Adequate Humoral Response (%)	P	N	Adequate Humoral Response (%)	P	N	Adequate Humoral Response (%)	P
Healthy	27	96.3	REF	25	100.0	REF	26	65.4	REF
All methotrexate	84	78.6	**0.039**	77	85.7	0.061	61	45.9	0.108
Monotherapy	47	76.6	**0.046**	47	85.1	0.088	35	54.3	0.438
All TNFi*	100	88.0	0.297	85	87.1	0.066	66	45.5	0.107
Monotherapy	63	92.1	0.664	55	87.3	0.092	40	52.5	0.322
Methotrexate +TNF	37	81.1	0.124	30	86.7	0.117	26	34.6	0.051
IL17	13	92.3	1.000	10	100.0	1.000	12	66.7	1.000
IL23^	12	100.0	1.000	10	100.0	1.000	4	75.0	1.000
JAKi	15	93.3	1.000	11	90.9	0.306	8	50.0	0.679
Rituximab	5	40.0	**0.008**	4	25.0	**0.001**	5	20.0	0.134
HCQ	15	93.3	1.000	13	84.6	0.111	16	43.8	0.210
Glucocorticoids#	15	86.7	0.287	12	91.7	0.324	13	53.8	0.508

* TNFi tumor necrosis factor inhibitor, IL-17 interleukin 17 inhibitor, IL-23 interleukin 23 inhibitor, JAKi janus kinase inhibitor, MTX methotrexate, HCQ hydroxychloroquine.
^Includes interleukin 12/23 blockers.
#Average glucocorticoid use at 4 weeks was 13.0 +/- 10.1 mg, at 3 months 13.3 +/- 10.8 mg, and at 6 months 12.0 +/- 9.7 mg of prednisone (or equivalent).

Supplemental Tables 7. Odds Ratios for achieving an adequate humoral response by IgG Spike Antibody at week 4.

4 Weeks	Unadjusted OR (95%CI)	P	Adjusted 1* OR (95%CI)	P	Adjusted 2 OR (95%CI)	p
Demographics						
Age> 65	0.40 (0.17, 0.99)	**0.047**	0.404 (0.17,0.99)	**0.047**	0.40 (0.16, 1.09)	0.500
Female	1.05 (0.48, 2.28)	0.902	1.09 (0.50, 2.39)	0.824	1.09 (0.50, 2.39)	0.824
Non-White	0.69 (0.30, 1.58)	0.378	0.59 (0.25, 1.40)	0.234	0.57 (0.24, 1.37)	0.209
Diagnosis						
Crohns	REF		REF		REF	
UC[X]	0.56 (0.09, 3.52)	0.535	0.57 (0.09, 3.61)	0.551	0.56 (0.09, 3.57)	0.541
PsO/PsA	0.33 (0.07, 1.61)	0.169	0.39 (0.08, 2.02)	0.264	0.35 (0.07, 1.81)	0.210
RA	0.22 (0.05, 1.02)	0.053	0.26 (0.05, 1.22)	0.088	0.17 (0.03, 0.92)	0.040
Other^	0.31 (0.05, 2.00)	0.219	0.36 (0.05, 2.35)	0.285	0.27 (0.04, 1.89)	0.189
Treatment						
MTX	0.27 (0.12, 0.60)	**0.001**	0.29 (0.13, 0.66)	**0.003**	0.27 (0.11, 0.63)	**0.002**
MTX-mono	0.33 (0.14, 0.75)	**0.008**	0.36 (0.15, 0.84)	**0.018**	0.32 (0.13, 0.80)	**0.014**
TNFi	0.97 (0.44, 2.14)	0.948	0.92 (0.42, 2.05)	0.846	0.92 (0.41, 2.07)	0.849
TNFi-mono	1.76 (0.64, 4.83)	0.271	1.59 (0.57, 4.43)	0.375	1.62 (0.57, 4.58)	0.364
MTX+ TNFi	0.51 (0.20, 1.29)	0.154	0.54 (0.21, 1.39)	0.201	0.54 (0.21, 1.39)	0.201
IL17/IL23[#]	3.50 (0.46, 26.88)	0.228	3.60 (0.47, 27.83)	0.219	3.60 (0.47, 27.84)	0.219
JAKi	1.94 (0.25, 15.33)	0.530	1.93 (0.24, 15.38)	0.533	1.93 (0.24, 15.39)	0.534
RTX	0.08 (0.01, 0.51)	**0.007**	0.09 (0.01, 0.60)	**0.012**	0.09 (0.01, 0.60)	**0.012**
Glucocorticoids	0.86 (0.18, 4.04)	0.853	0.74 (0.16, 3.53)	0.709	0.74 (0.15, 3.53)	0.241
MTX held[l]	3.50 (1.04, 11.75)	**0.043**	3.33 (0.98, 11.28)	0.053	3.17 (0.92, 10.88)	0.067

* Adjusted Model 1 adjusted for age, Adjusted Model 2 adjusted for age and sex.
[X]UC denotes ulcerative colitis, PsO/PsA psoriasis and/or psoriatic arthritis, RA rheumatoid arthritis, MTX methotrexate, MTX-mono methotrexate monotherapy, TNFi tumor necrosis factor inhibitor, TNFi-mono tumor necrosis factor inhibitor monotherapy, IL interleukin, JAKi janus kinase inhibitor, RTX rituximab, OR odds ratio, CI confidence interval.
^ Vasculitis, dermatomyositis, adult onset stills disease, sarcoidosis, and polymyalgia rheumatica.
[#]Includes interleukin 12/23 blockers.
[l]Methotrexate held odds ratio reflects the odds of achieving remission if at least one dose of methotrexate was held in the perivaccination period compared to those who continued methotrexate.

Supplemental Tables 8. Odds Ratios for achieving an adequate humoral response by IgG Spike Antibody at month 3.

3 Months	Unadjusted OR (95%CI)	P	Adjusted 1* OR (95%CI)	P	Adjusted 2 OR (95%CI)	p
Demographics						
Age> 65	0.65 (0.23, 1.88)	0.429	0.65 (0.23, 1.88)	0.429	0.65 (1.56, 0.23)	0.670
Female	1.55 (0.66, 3.62)	0.312	1.56 (0.67, 3.65)	0.308	1.56 (0.67, 3.65)	0.308
Non-White	0.69 (0.27, 1.75)	0.430	0.66 (0.25, 1.69)	0.381	0.57 (0.22, 1.52)	0.264
Diagnosis						
Crohns	REF					
UC[X]	0.56 (0.09, 3.57)	0.541	0.56 (0.09, 3.59)	0.545	0.54 (0.08, 3.47)	0.518
PsO/PsA	0.28 (0.06, 1.38)	0.117	0.30 (0.06, 1.50)	0.141	0.25 (0.05. 1.28)	0.097
RA	0.44 (0.09, 2.25)	0.326	0.46 (0.09, 2.39)	0.357	0.29 (0.05, 1.70)	0.169
Other[^]	0.28 (0.04, 1.84)	0.186	0.29 (0.04, 1.92)	0.199	0.21 (0.03, 1.50)	0.121
Treatment						
MTX	0.61 (0.26, 1.45)	0.264	0.64 (0.27, 1.54)	0.320	0.56 (0.23, 1.37)	0.204
MTX-mono	0.63 (0.25, 1.64)	0.347	0.67 (0.26, 1.75)	0.411	0.54 (0.19, 1.50)	0.236
TNFi	0.73 (0.31, 1.73)	0.479	0.70 (0.3, 1.67)	0.424	0.77 (0.32, 1.86)	0.557
TNFi-mono	0.80 (0.31, 2.06)	0.649	0.75 (0.29, 1.94)	0.548	0.83 (0.31, 2.23)	0.713
MTX+ TNFi	0.78 (0.25, 2.46)	0.670	0.08 (0.25, 2.53)	0.702	0.81 (0.25, 2.58)	0.719
IL17/IL23[ʃ]	NA[#]	NA	NA	NA	NA	NA
JAKi	1.26 (0.15, 10.27)	0.831	1.22 (0.15, 9.99)	0.854	1.10 (0.13, 9.14)	0.929
RTX	0.04 (0.00, 0.37)	**0.005**	0.04 (0.00, 0.40)	**0.006**	0.04 (0.00, 0.42)	**0.007**
Glucocorticoids	1.39 (0.17, 11.26)	0.758	1.29 (0.16, 10.54)	0.815	1.15 (0.14, 9.57)	0.897
MTX held[l]	8.33 (1.01, 68.87)	**0.049**	8.21 (0.99, 68.12)	0.051	9.00 (1.01, 79.87)	**0.049**

*Adjusted Model 1 adjusted for age, Adjusted Model 2 adjusted for age and sex
[X]UC denotes ulcerative colitis, PsO/PsA psoriasis and/or psoriatic arthritis, RA rheumatoid arthritis, MTX methotrexate, MTX-mono methotrexate monotherapy, TNFi tumor necrosis factor inhibitor, TNFi-mono tumor necrosis factor inhibitor monotherapy, IL interleukin, JAKi janus kinase inhibitor, RTX rituximab, OR odds ratio, CI confidence interval.
[^]Vasculitis, dermatomyositis, adult onset stills disease, sarcoidosis, and polymyalgia rheumatica.
[#]Could not converge due to empty cells.
[ʃ]Includes interleukin 12/23 blockers.
[l]Methotrexate held odds ratio reflects the odds of achieving remission if at least one dose of methotrexate was held in the perivaccination period compared to those who continued methotrexate.

Supplemental Tables 9. Odds Ratios for achieving an adequate humoral response by IgG Spike Antibody at month 6.

6 Months	Unadjusted OR (95%CI)	P	Adjusted 1* OR (95%CI)	P	Adjusted 2 OR (95%CI)	p
Demographics						
Age> 65	0.89 (0.40, 1.96)	0.770	0.89 (0.40, 1.96)	0.770	0.89 (1.27, 0.40)	0.700
Female	1.28 (0.70, 2.31)	0.424	1.27 (0.70, 2.31)	0.424	1.27 (0.70, 2.31)	0.424
Non-White	1.10 (0.58, 2.07)	0.779	1.09 (0.58, 2.06)	0.793	1.04 (0.54, 1.99)	0.904
Diagnosis						
Crohns	REF		REF		REF	
UC[X]	2.31 (0.70, 7.65)	0.170	2.31 (0.70, 7.65)	0.170	2.34 (0.70, 7.79)	0.165
PsO/PsA	0.83 (0.33, 2.12)	0.698	0.83 (0.32, 2.17)	0.707	0.77 (0.29, 2.04)	0.604
RA	1.05 (0.42, 2.62)	0.922	1.05 (0.41, 2.67)	0.920	0.86 (0.32, 2.34)	0.769
Other[^]	1.61 (0.49, 5.25)	0.430	1.61 (0.49, 5.27)	0.430	1.4 (0.41, 4.70)	0.591
Treatment						
MTX	0.51 (0.27, 0.97)	**0.039**	0.52 (0.27, 0.98)	**0.044**	0.50 (0.26, 0.96)	**0.037**
MTX-mono	0.89 (0.42, 1.89)	0.770	0.92 (0.43, 1.96)	0.827	0.89 (0.41, 1.95)	0.774
TNFi	0.48 (0.26, 0.90)	**0.022**	0.47 (0.25, 0.89)	**0.020**	0.47 (0.25, 0.89)	**0.020**
TNFi-mono	0.81 (0.40, 1.65)	0.563	0.79 (0.39, 1.62)	0.523	0.79 (0.39, 1.62)	0.521
MTX+ TNFi	0.35 (0.14, 0.83)	**0.018**	0.35 (0.15, 0.84)	**0.019**	0.35 (0.15, 0.84)	**0.019**
IL17/IL23[#]	1.79 (0.59, 5.39)	0.303	1.81 (0.60, 5.46)	0.295	1.83 (0.60, 5.56)	0.285
JAKi	0.76 (0.18, 3.15)	0.706	0.73 (0.18, 3.06)	0.671	0.74 (0.18, 3.07)	0.674
RTX	0.18 (0.02, 1.68)	0.134	0.19 (0.02, 1.70)	0.136	0.18 (0.02, 1.72)	0.138
Glucocorticoids	0.89 (0.29, 2.77)	0.843	0.86 (0.27, 2.70)	0.796	0.84 (0.27, 2.67)	0.774
MTX held[l]	5.60 (1.68, 18.70)	**0.005**	6.08 (1.75, 21.07)	**0.004**	5.98 (1.72, 20.79)	**0.005**

* Adjusted Model 1 adjusted for age, Adjusted Model 2 adjusted for age and sex

[X]UC denotes ulcerative colitis, PsO/PsA psoriasis and/or psoriatic arthritis, RA rheumatoid arthritis, MTX methotrexate, MTX-mono methotrexate monotherapy, TNFi tumor necrosis factor inhibitor, TNFi-mono tumor necrosis factor inhibitor monotherapy, IL interleukin, JAKi janus kinase inhibitor, RTX rituximab, OR odds ratio, CI confidence interval.

^ Vasculitis, dermatomyositis, adult onset stills disease, sarcoidosis, and polymyalgia rheumatica.

[#]Includes interleukin 12/23 blockers.

[l]Methotrexate held odds ratio reflects the odds of achieving remission if at least one dose of methotrexate was held in the perivaccination period compared to those who continued methotrexate.

Supplementary Table 10. Adequate humoral response rates by methotrexate dose.

	4 Weeks			3 Months			6 Months		
	N	Adequate humoral response[#] (%)	P	N	Adequate humoral response (%)	P	N	Adequate humoral response (%)	P
MTX* All									
High Dose	48	79.2		47	89.4		33	60.6	
Low Dose	35	80.0	1.000	30	83.3	0.499	24	54.2	1.000
MTX Monotherapy									
High Dose	31	80.6		32	87.5		22	68.1	
Low Dose	15	73.3	0.454	16	87.5	1.000	12	50.0	0.462
MTX +TNFi									
High Dose	17	76.5		14	93.3		11	45.5	
Low Dose	20	86.7	1.000	12	78.5	0.329	12	58.3	0.684

* MTX denotes methotrexate, TNFi tumor necrosis factor inhibitors. High dose defined as 15 mg or greater, low dose as 12.5 mg or less.
[#]Adeuqare humoral response defined as Spike IgG titer greater than or equal to 5000 RU/ml.

Supplementary Table 11. Humoral response rates in patients with IMID on tumor necrosis factor inhibitors compared to healthy controls and IMIDs not taking TNFis.

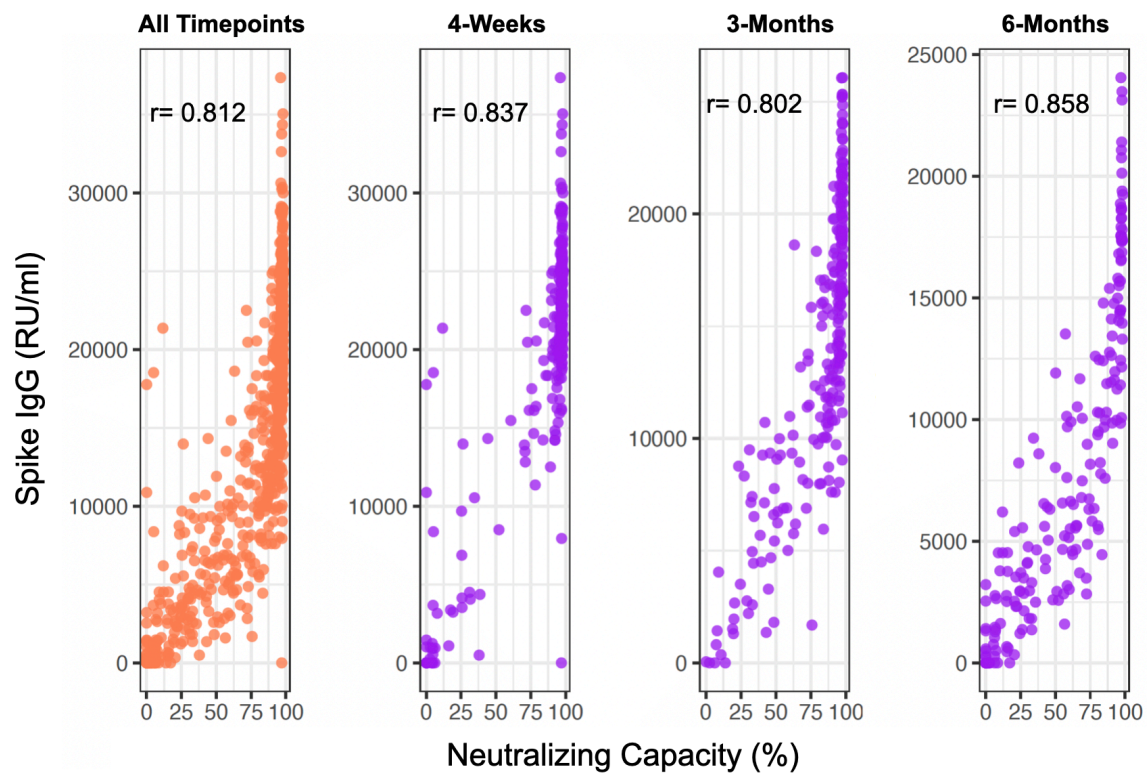|	4 Weeks				3 Months				6 Months			
	Healthy (n=27)	No TNFi (n=145)	Yes TNFi (n=100)	P	Healthy (n=25)	No TNFi (n=132)	Yes TNFi (n=85)	P	Healthy (n=26)	No TNFi (n=104)	Yes TNFi (n=66)	P
Age—mean (SD)	51.6 (13.2)	48.2 (16.1)	45.9 (14.8)	0.208	52.5 (13.2)	49.3 (15.8)	46.4 (14.9)	0.171	52.1 (13.1)	49.8 (15.7)	45.6 (14.7)	0.102
Female—n(%)	16 (59.3)	99 (68.3)	51 (51.0)	0.024	15 (60.0)	95 (72.0)	44 (51.8)	0.010	15 (57.7)	71 (68.3)	43 (65.2)	0.590
Race—n(%)				0.016				0.029				0.018
White	17 (63.0)	115 (79.3)	76 (76.0)		17 (68.0)	103 (78.0)	67 (78.8)		17 (65.4)	78 (75.0)	47 (71.2)	
Black	1 (3.7)	12 (8.3)	7 (7.0)		0 (0)	11 (8.3)	6 (7.1)			12 (11.5)	5 (7.6)	
Asian	9 (33.3)	8 (5.5)	11 (11.0)		8 (32.0)	8 (6.1)	7 (8.2)		9 (34.6)	8 (7.7)	9 (13.6)	
Other		9 (6.2%)	6 (6.0%)			9 (6.8)	5 (5.9)			6 (5.8)	5 (7.6)	
Hispanic—n(%)	1 (3.7)	27 (19.0)	9 (9.2)	0.029	1 (4.0)	26 (20.0)	8 (9.6)	0.034	1 (3.8)	18 (17.5)	7 (10.8)	0.150
Primary IMID*—n(%)				0.015				0.023				0.372
UC/Crohn's	—	48 (33.1)	36 (36.0)		—	43 (32.6)	32 (37.6)		—	31 (29.8)	19 (28.8)	
PsO/PsA	—	38 (26.2)	26 (26.0)		—	35 (26.5)	22 (25.9)		—	27 (26.0)	20 (30.3)	
RA	—	44 (30.3)	30 (30.0)		—	42 (31.8)	24 (28.2)		—	33 (31.7)	20 (30.3)	
Other+	—	15 (10.3)	8 (8.0)		—	12 (9.1)	7 (8.2)		—	13 (12.5)	7 (10.6)	
Other Medication—n(%)												
MTX	—	47 (32.4)	37 (37)	0.495	—	47 (35.6)	30 (35.3)	1	—	35 (33.7)	26 (39.4)	0.512
IL-17	—	13 (9.0)	0 (0)	0.001	—	10 (7.6)	0 (0)	0.007	—	12 (11.5)	0 (0)	0.004
IL-23`	—	12 (8.3)	0 (0)	0.002	—	10 (7.6)	0 (0)	0.007	—	4 (3.8)	0 (0)	0.158
JAKi	—	15 (10.3)	0 (0)	0.001	—	11 (8.3)	0 (0)	0.004	—	8 (7.7)	0 (0)	0.024
Glucocorticoids	—	9 (6.2)	6 (6.0)	1.000	—	7 (5.3)	5 (5.9)	1.000	—	8 (7.7)	5 (7.6)	1.000
Other DMARD#	—	26 (17.9)	13 (13.0)	0.375	—	24 (18.2)	13 (15.3)	0.712	—	24 (23.1)	12 (18.2)	0.564
Prior COVID-19—n(%)	5 (18.5)	31 (21.4)	17 (17.0)	0.710	4 (16.0)	25 (18.9)	15 (17.6)	0.970	5 (19.2)	16 (15.4)	11 (16.7)	0.861
Spike specific SARS-CoV-2 antibody titers—mean (SD)	20636.6 (5499.3)	20508.5 (8331.2)	19112.1 (7896.7)	0.065	16006.2 (5445.6)	15099.4 (6425.3)	11879.1 (5851.6)	<0.001	7583.1 (5033.2)	9229.5 (6519.2)	5987.6 (5879.3)	0.004
Adequate humoral response×—n(%)	26 (96.3)	128 (88.3)	88 (88.0)	0.531	25 (100.0)	119 (90.2)	74 (87.1)	0.16	17 (65.4)	66 (63.5)	30 (45.5)	0.053
Neutralization antibodies (%)—mean (SD)	90.9 (19.3)	83.9 (30.1)	79.4 (31.7)	0.011	87.4 (16.1)	83.9 (24.3)	73.4 (26.2)	<0.001	58.5 (29.4)	64.0 (34.7)	43.2 (34.8)	0.002
Adequate neutralization response×—n(%)	26 (96.3)	126 (86.9)	84 (84.0)	0.262	25 (100.0)	120 (90.9)	73 (85.9)	0.095	18 (69.2)	78 (75.0)	32 (48.5)	0.002

* IMID denotes immune mediate inflammatory disease, UC ulcerative colitis, PsO/PsA psoriasis and/or psoriatic arthritis, RA rheumatoid arthritis, TNFi tumor necrosis factor inhibitor, IL-17 interleukin 17 inhibitor, IL-23 interleukin 23 inhibitor, JAKi janus kinase inhibitor, MTX methotrexate, DMARD disease modifying anti-rheumatic drug.
+ Vasculitis, dermatomyositis, adult onset stills disease, sarcoidosis, and polymyalgia rheumatica.
# Leflunomide, sulfasalazine azathioprine, hydroxychloroquine, mercaptopurine.
× Adequate humoral response defines as antibody titers greater than 5000 (RU/ml). Adequate neutralization response defined as greater than 35%.
` Includes Interleukin12/23 blocking agents,

Supplementary Figure 1. Correlation between neutralizing capacity and Spike IgG titer overall and at each visit timepoint.